ORIGINAL ARTICLE

Efficacy and safety of vancomycin constant-rate infusion in the treatment of chronic Gram-positive bone and joint infections

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Objective: To evaluate the efficacy and safety of vancomycin constant-rate infusion over 24 h in the treatment of Gram-positive bone infections,

Methods: Vancomycin (40 mg/kg/day) was administered without a loading dose to 15 patients (12 male, three female) aged 23–90 years, weighing 46–85 kg, with postoperative chronic bone and joint infections. The 24-h dose was adjusted to maintain plasma levels between 25 and 35 mg/L. Mean duration of therapy was 6.2 months (4–8.5) via a portable infusion pump. Sites of infection included hip and femur (10), tibia (three), patella (one) and vertebrae (one). Sequestrectomy (two), removal of material (7/8 prosthetic hips, 1/5 metal implants) and debridement (two) were performed at the beginning of the treatment. Involved bacteria included *Staphylococcus aureus* (eight, six methicillin resistant), *S. epidermidis* (four methicillin-resistant), *Enterococcus faecalis* (one), *Enterococcus avium* (one) and *Streptococcus bovis* (one).

Results: MIC of vancomycin ranged from 1 to 4 mg/L. The mean vancomycin bone concentration when available was 67.7±38.9 μg/L. Based on a mean post-treatment follow-up of 14±4 months (6–20.6), cure was achieved in 10 patients (66.6%). Failures were related to the inability to remove the infected prosthesis (one) or implants (three) and to the persistence of a deep wound abcess (one). Adverse events included pruritus (four cases), tinnitus (two), mild transient elevation of creatinine level (three) and transient neutropenia (two). Vancomycin was maintained in all the patients.

Conclusions: Prolonged treatment with vancomycin constant-rate infusion is effective and safe for treatment of Gram-positive chronic bone and joint infections, providing that complete surgical débridement and prosthetic material removal are performed.

Key words: vancomycin, continuous intravenous infusion, chronic bone infection

Treatment of chronic Gram-positive bone and joint infections, whether due to trauma or surgical procedures, is a complex matter. Infection develops most often within a bone implanted with foreign material on which pathogens will adhere and enter a slow-growing phase, causing the foreign material to become coated with slime. This explains the very low success rate of treatments involving antibiotics alone. Thorough surgical treatment with removal of all suspect tissue and foreign material is required in addition to a prolonged course of antimicrobial therapy [1–4]. Most frequently involved pathogens include *Staphylococcus aureus* and *Staphylococcus epidermidis*. Methicillin-resistant strains have emerged with reduced susceptibility to quinolones, rifampicin and fosfomycin, which are also indicated in the treatment of bone infections [5]. In these instances, one of the remaining possibilities is to treat with glycopeptides (teicoplanin and vancomycin). The use of teicoplanin is limited by the existence of resistant strains [6,7]. The usual route of administration for vancomycin is repeated infusion. The other recognized possibility is continuous intravenous infusion, which

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complies best with the time-dependent activity of vancomycin by maintaining constant serum levels, and provides better tissue diffusion and tolerance [8]. This study was undertaken to evaluate the safety and efficacy of prolonged treatment with continuous vancomycin in chronic postoperative Gram-positive bone and joint infection.

PATIENTS AND METHODS

Study population

A patient was included in the study when the following criteria were met: clinical evidence of chronic bone and joint infection (chronic pain or draining sinuses from the involved areas of at least 1 month's duration); evidence that the initial infection appeared after an open fracture or elective orthopedic procedure; evidence of bone and joint infection on radiograph studies and/or radionuclide imaging (technetium polyphosphate, ^{99m}Tc and gallium scans), and/or magnetic resonance imaging; isolation of bacterial pathogens susceptible to vancomycin from a bone biopsy specimen or from aspirated joint fluid—the isolated pathogens were tested for in vitro susceptibility to vancomycin using standard methods, and MICs and MBCs for isolated organisms were determined by the standard tube dilution technique in Mueller-Hinton Broth; no history of allergy to glycopeptides.

Treatment protocol

All the patients were initially given a 40 mg/kg/day vancomycin infusion over 24 h without a loading dose. The 24 h dose was adjusted to maintain serum levels between 25 and 35 mg/L. An intravenous access system was implanted in each patient at the beginning of the treatment. Vancomycin was administered via an ambulatory delivery system to allow home antibiotic therapy. The system used was a Cadd 1 pump (Pharmacia Deltec). Additional antibiotics were given when the associated bacteria were resistant to vancomycin therapy. Whenever this was possible, surgical debridement and removal of foreign material was performed at the beginning of the treatment course.

Antibiotics were administered for 6 months. They were continued for over 6 months if the clinician believed that the therapy was effective but the infection had not totally resolved. Initial treatment administration was conducted on hospitalized patients who were monitored for 2 weeks before being discharged. They were subsequently treated at home with day-hospital follow-up. Regular replacement of the intravenous line and vancomycin cassette was ensured by day-hospital or home-care nurses trained in the use of this device.

Clinical monitoring and scheduling

Clinical assessment was conducted daily during hospitalization, then twice monthly until the end of treatment, and at the follow-up visits (3, 6 and 12 months). Pre-therapy tests included blood count, erythrocyte sedimentation rate, C reactive protein, creatinemia, glutamic pyruvic and glutamic oxaloacetic transaminases, alkaline phosphatases and urinalysis. They were repeated once a week during hospitalization, and then every 2 weeks and at follow-up visits. Audiometry tests were performed at the beginning and at the end of treatment and in case of any clinical symptom. Repeated imaging studies (radiographs, isotopic bone scans and, if possible, magnetic resonance imaging) were performed 3 months after the beginning of treatment, at the end of treatment, and between 3 and 6 months and again 12 months after ending treatment.

Vancomycin serum level was determined daily by fluorescence polarization immunoassay until the preset value was obtained, weekly during hospitalization, and twice a month on an outpatient basis. Whenever possible, bone samples were collected with the patient's consent by iliac crest biopsy. The specimens were pulverized and eluted into phosphate buffer and the supernatants were analyzed for vancomycin content by microbiological assay as well as on a simultaneous blood sample.

Determination of outcome

Success was defined as at least the following criteria being satisfied at the end of therapy and after a minimum follow-up period of 6 months: resolution of clinical symptoms; a gallium scan that appeared normal or showed significant improvement; and/or regression of focal inflammatory lesions on magnetic resonance imaging.

Persistence or recurrence of clinical symptoms and/or isolation of the same pathogen(s) were defined as failure.

RESULTS

Patient characteristics

Fifteen patients with Gram-positive chronic bone and joint infection received vancomycin. Duration of chronic infection ranged from 6 weeks to 10 years. There were 12 men and three women with a mean age of 61.7 years (range 23–90 years) and a mean weight of 70 kg (range 46–85 kg). Infection sites included hip and femur (10 patients), tibia (three patients), knee and patella (one patient) and vertebrae (one patient). The precipitating events were: prosthetic replacement in eight patients, tibial open fracture osteosynthesis in two patients, acetabular fracture osteosynthesis in two

Table 1 Characteristics of patients, treatment and outcome

Patient no.	Sex	Age (years)	Site of bone and joint infection	Underlying events	Duration of bone and joint infection	Foreign bodies in situ	Diagnosis procedure	Bacteria involved	Debridement	Removal of foreign body	Mean serum levels (range) (mg/L)	Therapy duration (days)	Failure (days post-treatment)	Follow-up (days)
1	M	56	Tibia	Open fracture osteosynthesis	6 years	Sequestrum	Bone biopsy	*E. avium*	Yes	Yes	36.7±6.1 (29–49)	180	No	400
2	M	76	Hip and femur	Prosthetic hip replacement	6 months	Prosthetic hip	Aspiration of joint fluid	MRSE	Yes	Yes	28.8±5.9 (19–40)	195	No	495
3	F	90	Hip and femur	Prosthetic hip replacement	2 years	Prosthetic hip and screw within the acetabulum	Aspiration of joint fluid	MRSA	Yes	No	30.2±6.3 (20–38.3)	184	Yes (53)	–
4	M	40	Tibia	Open fracture osteosynthesis	4 years	One screw	Bone biopsy	*Enterococcus faecalis*, *Escherichia coli* anaerobes, *Proteus mirabilis*	Yes sequestrectomy	No	26.7±3.7 (21–30.2)	120	Yes during treatment	–
5	M	44	Hip and femur	Prosthetic hip replacement	1 year	Prosthetic hip	Bone biopsy	MSSA	Yes	Yes	31.5±5.1 (25.5–42.7)	202	No	365
6	M	26	Pelvis and hip	Fracture osteosynthesis	2 months	Screws	Bone biopsy and aspiration of joint fluid	MRSA	No	No	29.7±6.8 (22–49)	180	No	390
7	M	23	Pelvis and hip	Fracture osteosynthesis	6 weeks	Screws and metal plates	Aspiration of joint fluid	MRSE	No	No	24.7±4 (20–30.4)	180	Yes (90)	–
8	M	47	Tibia	Open fracture osteosynthesis	15 months	Sequestrum	Bone biopsy	MRSE	Yes sequestrectomy	No	17.5±7.1 (10–35)	180	No	360
9	M	79	Hip and femur	Prosthetic hip replacement	8 months	Prosthetic hip	Arthrocentesis	MRSA	Yes	Yes	24.7±5.3 (19–39)	180	No	618
10	F	71	Hip and femur	Prosthetic hip replacement	8 months	Prosthetic hip	Bone biopsy	MRSE	Yes	Yes	31±6.4 (17–38)	195	No	350
11	M	65	Hip and femur	Prosthetic hip replacement	10 years	Prosthetic hip pin and steel wires	Bone biopsy	*Streptococcus bovis*	Yes	Yes	25.1±4.6 (18.5–34.5)	196	No	425
12	M	74	Hip and femur	Prosthetic hip replacement	2 years	Prosthetic hip	Bone biopsy	MRSA	Yes	Yes	29.4±4.6 (23–37)	180	No	570
13	M	73	Hip and femur	Prosthetic hip replacement	1 year	Prosthetic hip	Bone biopsy	MSSA	Yes	Yes	37.3±9.3 (23.5–49.5)	180	Yes (30)	–
14	M	69	Knee	Knee arthroplasty	6 weeks	Trochlear shield	Aspiration of joint fluid	MRSA	Yes	No	26.9±5.9 (18–43.5)	235	Yes (40)	–
15	F	81	Vertebra	Laminectomy for narrow lumbar canal	6 weeks	–	Bone biopsy	MRSA	Yes	No	33.9±7.2 (21.8–42.6)	180	No	180

MRSE=methicillin-resistant *Staphylococcus epidermidis*.
MSSA=methicillin-sensitive *Staphylococcus aureus*.
MRSA=methicillin-resistant *Staphylococcus aureus*.

patients, closed tibial fracture osteosynthesis in one patient, knee joint arthroplasty in one patient, and laminectomy for lumbar canal stenosis in one patient (Table 1).

Patients were treated with vancomycin for a mean duration of 184 days (range 120–235). Concomitant surgical management included sequestrectomy in two patients, removal of prosthetic hip in seven patients, removal of metal implant in one patient, debridement without removal of the hip prosthesis in one patient and perivertebral abscess drainage in one patient. Among patients with prosthesis removal, two had a secondary hip replacement through a two-stage surgical procedure. Reimplantation of a prosthesis was not possible in the other patients, due to the severity of adjacent bone lesions.

Bacteriological results

Eighteen pathogens were isolated from the 15 patients either from bone biopsy, collected at the time of surgical debridement, or needle aspirate. Bacteria involved were *Staphylococcus aureus* (eight), among which six were resistant to methicillin (MRSA), *Staphylococcus epidermidis* (four), all resistant to methicillin (MRSE), *Streptococcus bovis* (one), *Enterococcus avium* (one), and *Enterococcus faecium* (one). In one patient, *Proteus mirabilis*, *E. coli* and *Bacteroides* sp. were recovered from the bone biopsy in addition to *Enterococcus faecalis*. MICs of vancomycin for the Gram-positive isolates ranged from 1 to 4 mg/L.

Vancomycin dosage and serum and bone vancomycin levels

After initial dose adjustment, the mean weight-related dosage ranged from 26 mg/kg to 47 mg/kg for 14 patients. One patient with prior renal impairment received a daily dose of 15 mg/kg. Mean concentration as measured by fluorescent polarization assay was 28.7± 4.5 mg/L with a median of 28 mg/L. An iliac crest bone biopsy was performed in six patients after a treatment course of at least 15 days. Concentration of vancomycin by the microbiological method after multiple extractions gave a mean concentration of 67.7±38.9 μg per gram of non-infected bone tissue. Because of the small size of the bone samples, separate concentration of vancomycin in cortical bone and cancellous bone was not performed.

Outcome

Based on a mean post-treatment follow-up of 14±4 months (range 6–20.6), the infection was arrested in 10 patients (66.6%) (Table 1).

One primary failure occurred during treatment. This patient (no. 4) had a 4-year history of sepsis of a tibial fracture site with a double sinus and a large sequestrum. Removal of the sequestrum was performed prior to treatment. Several organisms were involved: *Enterococcus faecalis*, *E. coli*, *Proteus mirabilis* and *Bacteroides* sp. In addition to vancomycin, this patient received ceftriaxone and metronidazole. The course was initially favorable, with partial subsidence of sinus discharge and partial closure of the sinus orifices. After a treatment period of 4 months, there was a recurrence of sinus discharge with re-isolation of the initial pathogens and no improvement on radionuclide and magnetic resonance imaging. Four secondary failures occurred with a mean delay of 53 days (range 30–90) after discontinuation of therapy. The first patient (no. 3) presented with sepsis related to a hip prosthesis with involvement of adjacent bone tissue. Surgical treatment consisted of drainage of a periprosthetic abscess due to MRSA. Vancomycin treatment resulted in sinus closure, while pain and inflammation subsided. Relapse occurred 53 days after treatment was discontinued, with reopening of the sinus orifice and re-isolation of the same pathogen. The second patient (no. 6) presented with sepsis following pelvic, acetabular and greater trochanter osteosynthesis after multiple fractures. Thorough surgical debridement was not possible. Treatment resulted in closure of the draining sinus and regression of the inflammatory syndrome. It was considered as a failure 3 months after discontinuation when radiologic findings showed destruction of the hip joint with a dense and heterogeneous aspect of the acetabulum and iliac bone and persisting hyperfixation on the gallium scan. The third patient (no. 14) had chronic MRSA infection of the knee following implantation of a trochlear shield. Surgical treatment consisted of total synovectomy and condylotibial arthroplasty with no removal of foreign material. After 6 months of treatment, the inflammatory syndrome had completely resolved. Persistence of hyperfixation within the femorotibial joint space on the gallium scan led to prolongation of treatment for two more months. Both needle aspirates of the knee joint performed during treatment because of a mild effusion were sterile. Recurrence was noted 40 days after stopping treatment, when major effusion of the knee joint developed with re-isolation of the same pathogen.

The last treatment failure (no. 13) concerned a patient with MSSA prosthetic hip infection. Upon removal of the prosthesis, a large abscess was discovered adjacent to the greater trochanter. At the end of the antibiotic treatment course, the inflammatory signs had resolved, gallium fixation was normal and there was no sign of pus collection. A month later the patient had mild pyrexia and elevated C reactive protein. Ultrasonic examinations showed a hypoechogen collection

around the trochanter from which the same MSSA was recovered with an MIC of 1 μg/mL and an MBC of 16 μg/mL.

Adverse effects

Adverse events occurring in our patients were analyzed by the Committee on Safety of Medicine of Nice.

Five patients experienced adverse events with a probable relation to vancomycin: three (nos. 12, 13 and 14) had a moderately increased creatinine serum level (grade 1) which appeared after the second month of treatment for two patients and after the seventh month for the last patient, with vancomycin levels ranging from 40 to 43.5 mg/L; two patients had transient neutropenia, and in one patient (no. 6) neutropenia (550 neutrophils/mm^3) developed after 20 days of treatment and was associated with a high vancomycin serum level (49.5 mg/L). Treatment was discontinued until the neutrophil count returned to normal (6 days). No recurrence of neutropenia was noted after reintroduction of vancomycin at a lower dose. In the other patient (no. 8) the drop in neutrophil count (900/mm^3) occurred after 6 weeks' treatment duration. Vancomycin serum level was then 35 mg/L. This patient complained at the same time of tinnitus. The audiogram showed a high-frequency 10-dB hearing loss in the left ear which could be related to vancomycin administration. Adverse events having a possible relation with vancomycin included: pruritus, which appeared in four patients between 30 and 120 days of treatment and resolved spontaneously in one patient and after antihistamine therapy in the other three; and transient tinnitus in one patient at 75 days of treatment with no change on the audiogram. At least four patients developed dermatophytosis of the face, thorax, inguinal fold, and scalp which resolved with specific topical treatment. One patient presented with an infection of the indwelling intravenous access system at the end of treatment which required removal of the infected material. *Proteus mirabilis* was the involved pathogen.

No treatment was permanently discontinued. In the three patients with mild creatinemia elevation, daily dosage of vancomycin was adjusted to maintain serum levels within the preset values. In the patient with neutropenia and tinnitus, dosage was reduced to 20 mg/kg/day, resulting in resolution of auditory and blood count disorders while maintaining a serum level of vancomycin of 20 mg/L.

DISCUSSION

This study confirms that prolonged continuous vancomycin infusion is effective for the treatment of chronic bone and joint infections caused by Gram-positive bacteria, including methicillin-resistant staphylococci. Our success rate after a mean follow-up of 14 months was 66%. These results are comparable to those obtained with teicoplanin which offers an alternative for the treatment of MRSA chronic osteitis [9,10]. Few data are available concerning the treatment of bone infection with vancomycin. Animal studies on either the rabbit or the rat model show diverging results. On a model involving MSSA, Norden and Shaffer [11] demonstrated poor efficacy of vancomycin and its possible relation to the low oxygen tensions found in osteomyelitic bone. On the other hand, on a model involving MRSA, vancomycin resulted in sterilization of infected bone in 40% of the animals [12]. In the small series of patients reported in the literature [13,14], vancomycin is used in repeated infusion of variable dosage and treatment duration. In Fitzpatrick's series [14], six out of 10 patients experienced no recurrence during a 2-year follow-up period. Nevertheless, repeated administration of the antibiotic, requiring hospitalization, is a limiting factor. Several arguments lead to the use of continuous vancomycin infusion. First, it ensures better tissue diffusion. Data are scarce concerning diffusion within bone tissue. However, results of a study conducted by Desplaces et al [15] on a limited number of non-infected samples show that concentrations obtained after continuous infusion are markedly higher (65.6±36 μg per gram of bone tissue (median, 56; range 16/cortical bone to 130/cancellous bone)), than those obtained with discontinuous infusion [16–18]. We have obtained similar results with iliac crest biopsy samples. Second, several clinical studies have demonstrated the efficacy of continuous vancomycin infusion in various MRSA infections [19]. In the published series, administered doses ranged from 30 to 50 mg/kg/day with or without a loading dose [8,15,19]. In fact, dosage must be correlated with the required concentration at the site of infection. This should theoretically be 8–10 times the MIC for the involved pathogens [20]. Third, tolerance is improved; no incidence of red man syndrome has been reported in any of the studies. In our series, the clinical and biological tolerance of vancomycin continuous infusion over 6 months was satisfactory. No treatment course was permanently discontinued because of major intolerance. Adverse effects with a probable relation to vancomycin included leucopenia, mild elevation of creatinemia and tinnitus. These disturbances were associated with vancomycin serum levels >35 mg/L during regular follow-up. Dose readjustment resulted in all cases in partial or complete regression of the observed abnormalities. Biological disturbances disappeared upon discontinuation of treatment in each case. The patient (no. 8) whose audiogram had revealed

mild ototoxicity remained stable and even improved at the last check-up visit. Nevertheless, long-term administration of vancomycin requires a reliable intravenous line and the fitting of a continuous infusion system. The Cadd 1 pump is a peristaltic pump that delivers the drug from a cassette which generally contains a 72 h dose of vancomycin, thus restricting the number of manipulations. Finally, the use of a small portable computer-controlled pump allows the patient not only to leave the hospital but also to assume many normal activities of daily life.

Our study, like those of Fitzpatrick et al [14], shows that success depends on the initial surgical treatment (debridement and/or removal of foreign material) associated with medical treatment. Outcome was successful in seven of the eight patients in whom removal of the foreign material was performed initially, and in three patients with either initial sequestrectomy or abscess drainage. Treatment failures were related to inadequate debridement and persistence of foreign material (three patients) and irradiated bone (one patient). In the presence of foreign material, various factors may account for treatment failure: non-penetration of the antibiotic within the biofilm, changes in the immune response in the presence of foreign material, slow-growing pathogens. Darouiche's study of an in vitro model for prosthesis-related infection shows that the failure of vancomycin to cure prosthesis infection is not due to its poor penetration in the biofilm, but is related to a low antimicrobial effect on bacteria within the biofilm environment [21].

The duration of antibiotic treatment in chronic bone and joint infection has not been entirely determined. Recommendations vary, ranging from a few weeks to several years [2]. Moreover, there is no consensus on the necessity of continuing antibiotic therapy after removal of foreign material or extensive curettage, or on its duration. Nevertheless, difficulties in removing all infected bone during surgical debridement, resulting in a high recurrence risk due to microscopic infection, underline the necessity of a prolonged treatment [22]. Furthermore, in case of infected prosthesis, a short treatment course associated with a one- or two-stage replacement procedure resulted in a success rate of only 35%, while it reached 90% with long-term antibiotic treatment [23,24].

In conclusion, although our study concerns a limited number of patients, prolonged treatment with vancomycin continuous intravenous infusion appears to be safe and effective for the treatment of Gram-positive chronic bone infection, providing thorough surgical treatment is initially performed, including removal of all foreign material. It ensures higher bone tissue concentrations than those obtained with intermittent infusion and allows outpatient treatment via an ambulatory delivery system, thus improving the patient's comfort and reducing the overall cost of treatment.

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